Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of the Claims:

1. (Currently amended) A process for preparing ~~recombinant~~ adenovirus, the process comprising:
   (a) preparing a culture of producer cells in a selected media;
   (b) infecting producer cells in the culture with the~~recombinant~~ adenovirus, wherein the producer cells are infected between mid-log phase of growth and stationary phase of growth; and
   (c) harvesting ~~recombinant~~ adenovirus from the cell culture.

2. (Currently amended) The process of claim [[1]]30, wherein the producer cells are infected with the adenovirus between late-log phase and stationary phase of growth.

3. (Currently amended) The process of claim 1, wherein the producer cells are essentially homogeneous with respect to [[cell]]the phase of cell growth.

4. (Original) The process of claim 1, wherein the producer cells are perfused for at least a portion of the time that the cells are cultured.

5. (Original) The process of claim 4, wherein the producer cells are perfused at a rate that will maintain a glucose level of between about 0.5 and about 3.0 gm glucose/liter.

6. (Original) The process of claim 5, wherein the producer cells are perfused at a rate that will maintain a glucose level of between about 0.7 and about 2.0 gm glucose/liter.

7. (Original) The process of claim 6, wherein the producer cells are perfused at a rate that maintains a glucose level of between about 1 and about 1.5 gm glucose/liter.

8. (Original) The process of claim 1, wherein the producer cells are seeded into the culture medium and allowed to attach to a culture surface for between about 3 hours and about 24 hours prior to infection with adenovirus.

9. (Original) The process of claim 1, wherein the culture medium is at least partially recirculated during the adenovirus infection step.

10. (Original) The process of claim 1, wherein the culture medium is seeded with between about 0.5×10^4 and about 3×10^4 cells/cm2.

11. (Original) The process of claim 10, wherein the culture medium is seeded with between about 7.5×10^3 and about 2.0×10^4 cell/cm2.

12. (Original) The process of claim 11, wherein the culture medium is seeded with between about 9×10^3 and 1.5×10^4 cells/cm2.

13. (Original) The process of claim 1, wherein the harvested adenovirus is subjected to purification and placed into a pharmaceutically acceptable composition.

14. (Original) The process of claim 13, the adenovirus is purified by steps which include chromatography.

15. (Original) The process of claim 14, wherein the chromatography step involves subjecting the adenovirus to more than one chromatographic separations.

16. (Original) The process of claim 14, wherein the chromatography step involves subjecting the adenovirus to only one chromatographic separation.

17. (Original) The process of claim 16, wherein the chromatographic separation includes ion-exchange chromatography.

18. (Currently amended) The process of claim 1, wherein said ~~recombinant~~ adenovirus is a replication-deficient adenovirus encoding a selected gene operably linked to a promoter.

19. (Original) The process of claim 18, wherein said replication deficient adenovirus is lacking at least a portion of the E1 region.

20. (Original) The process of claim 19, wherein said producer cells complement the growth of replication deficient adenovirus.

21. (Original) The process of claim 1, wherein said producer cells are selected from the group consisting of 293, PER.C6, 911 and IT293SF cells.

22. (Original) The process of claim 21, wherein said producer cells are 293 cells.

23. (Original) The process of claim 18, wherein said selected gene is selected from the group consisting of antisense *ras*, antisense *myc,* antisense *raf,* antisense *erb,* antisense *src,* antisense *fms,* antisense *jun,* antisense *trk,* antisense *ret,* antisense *gsp,* antisense *hst,* antisense *bcl* antisense *abl,* Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, zac1, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11 IL-12, GM-CSF G-CSF, mda-7, thymidine kinase or p53.

24. (Original) The process of claim 23, wherein said selected gene is a p53 gene.

25. (Original) The process of claim 18, wherein said promoter is an SV40 IE, RSV LTR, β-actin, CMV-IE, adenovirus major late, polyoma F9-1, or tyrosinase promoter.

26. (Original) The process of claim 1, wherein the adenovirus is harvested by steps that include lysing the producer cells by means other than freeze-thaw.

27. (Original) The process of claim 26, wherein the producer cells are lysed by means of a detergent lysis.

28. (Original) The process of claim 26, wherein the producer cells are lysed by means of autolysis.

29. (Currently amended) The process of claim 1, further comprising purifying the harvested adenovirus to obtain a purified ~~recombinant~~ adenovirus composition having one or more of the following properties:

(a) a virus titer of between about 1×10^9 and about 1×10^{13} pfu/ml;

(b) a virus particle concentration between about 1×10^{10} and about 2×10^{13} particles/ml;

(c) a particle:pfu ratio between about 10 and about 60;

(d) having less than 50 ng BSA per 1×10^{e12} viral particles;

(e) between about 50 pg and 1 ng of contaminating human DNA per 1×10^{12} viral particles,

(f) a single HPLC elution peak consisting essentially of 97 to 99% of the area under the peak.

30. (New) The process of claim 1, wherein infecting producer cells in the culture with the adenovirus occurs in a bioreactor system, a microcarrier culture system, a multiplate culture system, a perfused packed bed reactor system, or a microencapsulation culture system.

31. (New) The process of claim 29, further comprising formulating the purified adenovirus composition into a pharmaceutically acceptable composition.

32. (New) The process of claim 31, wherein the pharmaceutically acceptable composition is comprised in a pharmaceutically acceptable carrier.

33. (New) The process of claim 31, wherein the pharmaceutically acceptable composition is administered to a subject.

34. (New) The process of claim 33, wherein the subject is a mammal.

35. (New) The process of claim 34, wherein the mammal is a human or a mouse.

36. (New) The process of claim 33, wherein administering is intravenously, intradermally, intramuscularly, intraarterially, intralesionally, percutaneously, subcutaneously, or by inhalation.

37. (New) The process of claim 36, wherein administering is intratumorally.

38. (New) The process of claim 1, wherein the adenovirus is a recombinant adenovirus.

39. (New) The process of claim 1, wherein the producer cells are cultured in a bioreactor system.

40. (New) The process of claim 39, wherein the bioreactor system is a stirred tank reactor.

41. (New) The process of claim 39, wherein the bioreactor system is a airlift reactor.

42. (New) The process of claim 39, wherein the bioreactor system is a sparged bioreactor.

43. (New) The process of claim 1, wherein the producer cells are cultured in a microcarrier culture system.

44. (New) The process of claim 1, wherein the producer cells are cultured in a multiplate cell culture system.

45. (New) The process of claim 1, wherein the producer cells are cultured in a perfused packed bed reactor system.

46. (New) The process of claim 1, wherein the producer cells are cultured in a microencapsulation culture system.

47. (New) In a method for producing adenovirus that includes culturing producer cells and infecting the cultured producer cells with an adenovirus, wherein the improvement comprises infecting said producer cells with the adenovirus when the cells in culture are between mid-log phase of growth and stationary phase of growth.

48. (New) A method of claim 47, wherein the improvement comprises infecting the cultured producer cells in a bioreactor system, a microcarrier culture system, a multiplate culture system, a perfused packed bed reactor system, or a microencapsulation culture system.

49. (New) A method of claim 47, wherein the improvement further comprises harvesting adenovirus from the cell culture.

50. (New) A method of claim 47, wherein the improvement further comprises infecting producer cells in a culture with adenovirus between late-log phase of growth and stationary phase of growth.

51. (New) A method of claim 47, wherein said adenovirus is a recombinant adenovirus.

52. (New) A method of claim 51, wherein said recombinant adenovirus comprises a selected gene operably linked to a promoter.

53. (New) A method of claim 47, wherein said adenovirus is a replication-deficient adenovirus.

54. (New) A method of claim 53, wherein said replication deficient adenovirus is lacking at least a portion of the E1 region.

55. (New) A method of claim 47, wherein said producer cells complement the growth of replication deficient adenovirus.

56. (New) A method of claim 55, wherein said producer cells are selected from the group consisting of 293, PER.C6, 911 and IT293SF cells.

57. (New) A method of claim 56, wherein said producer cells are 293 cells.

58. (New) A method of claim 47, wherein the producer cells are essentially homogeneous with respect to the phase of cell growth.

59. (New) A method of claim 52, wherein said selected gene is selected from the group consisting of antisense *ras*, antisense *myc,* antisense *raf,* antisense *erb,* antisense *src,* antisense *fms,* antisense *jun,* antisense *trk,* antisense *ret,* antisense *gsp,* antisense *hst,* antisense *bcl* antisense *abl,* Rb, CFTR, p16, p21, p27, p57, p73, C-CAM, APC, CTS-1, zac1, scFV *ras*, DCC, NF-1, NF-2, WT-1, MEN-I, MEN-II, BRCA1, VHL, MMAC1, FCC, MCC, BRCA2, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11 IL-12, GM-CSF G-CSF, mda-7, thymidine kinase or p53.

60. (New) A method of claim 59, wherein said selected gene is a p53 gene.

61. (New) A method of claim 52, wherein said promoter is an SV40 IE, RSV LTR, β-actin, CMV-IE, adenovirus major late, polyoma F9-1, or tyrosinase promoter.

62. (New) A method of claim 49, wherein the improvement further comprises purifying the harvested adenovirus to obtain a purified adenovirus composition having one or more of the following properties:

(a) a virus titer of between about 1×10^9 and about 1×10^{13} pfu/ml;

(b) a virus particle concentration between about 1 x 10^{10} and about 2 x 10^{13} particles/ml;

(c) a particle:pfu ratio between about 10 and about 60;

(d) having less than 50 ng BSA per 1 x 10^{e12} viral particles;

(e) between about 50 pg and 1 ng of contaminating human DNA per 1 x 10^{12} viral particles,

(f) a single HPLC elution peak consisting essentially of 97 to 99% of the area under the peak.

RESPONSE TO THE OFFICE ACTION DATED OCTOBER 3, 2003

A. Status of the Claims

Claims 1-29 were pending at the time of the Action. Claims 1-3, 18 and 29 have been amended herein. New claims 30-62 have been added. Support for amendments to the claims may be found in the specification and the claims as originally filed. No new matter has been added. Therefore, the claims pending in the present application are claims 1-62.

B. Disclaimer of Priority

Applicants have deleted the priority paragraph on page 2 of the specification pursuant to MPEP 201.11, section III. G. at 200-73, entitled "Reference to Prior Applications - Deleting Benefit Claims," which states:

"As a result of the 20-year patent term [measured from the filing date of the earliest U.S. application for which benefit under 35 U.S.C. 120, 121, or 365(c) is claimed], **it is expected,** in certain circumstances, that applicants may cancel their claim to priority **by amending the specification or submitting a new application data sheet** (no supplemental declaration is necessary) to delete any references to prior applications." *Id.* (emphasis added).

C. Rejection of the Claims 1-3, 8-25 and 29 Under 35 U.S.C. §103(a) Is Overcome

Claims 1-3, 8-25 and 29 are rejected under 35 U.S.C. §103(a) as being unpatentable over Huyghe *et al.*, Zhang *et al.*, and Leu *et al.* The Action contends that claims 1-3 and 8-29 are drawn to a method of preparing a recombinant adenovirus by allowing a culture of producer cells (293) to attach to a culture surface, infecting the producer cells with recombinant adenovirus between late-log and stationary phase. The Action further contends that Leu *et al.* teach a method of producing large quantities of virus by allowing uniform attachment of cells, growing the cells to late-log phase with medium replenishment to provide adequate cell nutrition and infecting the cells at late-log phase and harvesting the virus. The Action also argues that one of

ordinary skill in the art at the time the invention was made would have been motivated to have propagated the adenovirus encoding p53 of Huyghe *et al.* and Zhang *et al.* with the cell culture method steps of infection taught by Leu *et al.* The Action also alleges that Leu *et al.* teach that a wide range of viruses may be propagated to generate vaccines using the methods steps. The Applicants respectfully traverse this rejection.

In the first instance, Applicants point out that the Examiner has incorrectly characterized the broadest claim of the present invention as being drawn to a method of preparing a recombinant adenovirus by allowing a culture of producer cells to attach to a culture surface. Claim 1, which has been broaden, recite "A process for preparing adenovirus, the process comprising: (a) preparing a culture of producer cells in a selected media; (b) infecting producer cells in the culture with the adenovirus, wherein the producer cells are infected between mid-log phase of growth and stationary phase of growth; and (c) harvesting adenovirus from the cell culture."

In a further instance, the Applicants point out that the combination of the references of Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* fails to meet the necessary criteria for establishing a *prima facie* case of obviousness of the present invention.

In order to establish a prima *facie* case of obviousness, three basic criteria must be met: 1) there must be some suggestion of motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. *MPEP* § 2142. *See also In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed Cir. 1991) (emphasizing that

the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be both found in the prior art, and not based on applicant's disclosure).

1. ***There is no suggestion or motivation to combine the references of Leu et al. Huyghe et al., and Zhang et al.***

One criteria necessary in establishing a prima facie case of obviousness is that there be some suggestion or motivation to combine Leu *et al.* with the teachings of Huyghe *et al.* and Zhang *et al.* to prepare adenovirus as claimed in the instant invention. The Action contends there is such suggestion or motivation, however, this argument is faulty for several reasons.

a. Leu et al. is replete with reference to hepatitis A virus

The Action contends that one of ordinary skill in the art at the time the invention was made would have been motivated to have propagated the adenovirus encoding p53 of Huyghe *et al.* and Zhang *et al.* with the cell culture method steps of infection taught by Leu *et al.* However, the Action does not identify why that skilled artisan would turn to the Leu *et al.* reference for the cell culture method steps of ***adenoviral*** infection. There is no credible reason why the skilled artisan, armed with the teaching of Huyghe *et al.* and Zhang *et al.*, would turn to the Leu *et al.* reference to achieve production levels of **adenovirus**, as in the claimed invention. Applicants point out that there is no mention made of adenovirus throughout the entire Leu *et al.* reference. Rather, Leu *et al.* is replete with references to hepatitis A virus. Specifically, Leu *et al.* teach a method of producing large quantities of hepatitis A virus (HAV). However, the present invention is specific to adenovirus.

As would be known by anyone of ordinary skill in the art, hepatitis A virus is structurally and functionally distinct from that of adenoviruses. The distinctions between hepatitis A virus and adenovirus are set forth in the attached declaration of one of the inventors, Dr. Shuyuan Zhang who has extensive research experience in the field (see *curriculum vitae*; see Exhibit 1).

b. Hepatitis A virus and adenovirus have distinct properties

The hepatitis A virus, based on its structure and biological properties, is classified as belonging to the viral family *Picornaviridae*. An adenovirus, on the other hand, has a different structure and biological properties and is classified as belonging to the viral family *Adenoviridae*. These distinctions are supported by the declaration of Dr. Shuyuan Zhang ("Zhang Declaration"; attached hereto as Appendix A) and are discussed below.

Adenoviruses contain double-stranded DNA approximately 36 kb in length. They are covered by a capsid 70-100 nm in diameter. This differs from hepatitis A viruses in that hepatitis A viruses contain positive single-stranded RNA of approximately 7.2–8.4 kb in length. hepatitis A viruses are comprised of a small, 27-32 nm, protein capsid. The capsid is composed of 60 protein subunits, each consisting of four polypeptides VP1-VP4. The RNA strand is covalently bonded to a noncaspid viral protein (VPg) at its 5' end and to a polyadenylated tail at its 3' end. Zhang Declaration, ¶5.

Further, mature adenovirus capsid is composed of 252 protein subunits of which 240 are hexons and 12 are pentons. A fiber protein projects from the base of the pentons. The adenovirus core is composed of the linear double stranded DNA and four virus coded core proteins that specifically bind to the DNA. Adenoviruses encode a DNA polymerase but depend on the host cells for many of the other functions involved in synthesis of DNA. DNA replication is complex and distinct from that of other viruses; it involves covalently bound proteins at the ends of the DNA and circularization. Transcription is also complex, involving early and late genes distributed randomly along both strands of the DNA. Replication and assembly occur in the nucleus. After adenoviral replication, the adenovirus is assembled inside the host cell's nucleus resulting in the optimal stability for this virus being at a pH between 7.0-8.5. Hepatitis

A viruses on the other hand, are heat and acid stable, and relatively detergent resistant. Stability of Hepatitis A viruses is best achieved at a pH of 3.0 or lower. These features of hepatitis A virus are not shared by adenovirus, and would strongly suggest that purification methods useful for Hepatitis A viruses would not necessarily be relevant to adenovirus. Zhang Declaration, ¶6.

In contrast to adenoviruses, hepatitis A viruses undergo replication and assembly in the cytoplasm. Their RNA acts as a messenger to synthesize viral macromolecules. Viral RNA replicates in complexes associated with cytoplasmic membranes via two distinct, partially double-stranded RNAs - the "replicative intermediates." One complex uses the sense RNA strand, and the other uses the antisense RNA strand as a template. RNA replication involves the synthesis of a complementary RNA which serves as a template for genome RNA synthesis. Genome RNA also serves as mRNA, being translated into a polyprotein that is cleaved into all the viral proteins including those proteins that serve as enzymes for specific cleavage. Zhang Declaration, ¶7.

Another difference between adenoviruses and hepatitis A viruses is that the negative DNA strand of the double-stranded DNA of adenoviruses is directly transcribed into viral mRNA, whereas the positive single-stranded RNA of hepatitis A viruses is copied into negative RNA that is transcribed into viral mRNA. Zhang Declaration, ¶8.

Adenoviruses and Hepatitis A viruses are further distinct in their routes and manner of infection of a cell. Infection of hepatitis A virus occurs at a specific time in growth from that of adenovirus. Hepatitis A virus infection is nonlytic and usually persists indefinitely. The initial stage of infectivity of hepatitis A virus occurs during the lag period due to residual inoculum virus which fails to be uncoated. During this stage, viral RNA is released and synthesis of protein and RNA occurs. This is followed by an exponential period at which the concentration

of infectivity doubles and leads to a plateau period. Upon infection RNA synthesis decreases in the host cell and subsequently synthesis of viral RNA in the cytoplasm occurs. Thus, while inhibiting cellular RNA synthesis in the nucleus, viral RNA synthesis in the cytoplasm occurs. This is followed by the inhibition of cellular protein synthesis and rapid synthesis of viral proteins. Following a decrease of viral protein synthesis, leakage of intracellular components occurs leading to cell death. Zhang Declaration, ¶9.

Adenovirus infection, on the other hand, is lytic and occurs at high multiplicities. The adenovirus replicative cycle is divided into early and late phases with the late phase beginning at the onset of viral DNA replication. Host cell DNA and protein synthesis are inhibited in cells infected with most adenoviruses as viral DNA synthesis begins. Infection involves the fiber of the virus attaching to a specific receptor on the cell membrane. A decrease in pH alters the surface of the virion resulting in rupture of the endocytic vesicle which releases the virion into the cytoplasm. Adenoviruses, specifically human adenoviruses, remain cell-associated after the production of the new virus is completed. This virus-to-cell association makes it possible for concentration of large quantities of viruses. Zhang Declaration, ¶10.

Further evidence of the above stated distinctions between hepatitis A virus and adenovirus may be found in any reference of virology, for example, in "Fields Virology" (B. N. Fields, Editor, Vol. 2, 3rd Ed., Lippincott Raven Publishers, 1996; Vol. 1, 4th Ed., Lippincott Williams, Wilkins Publishers, 2001), "The Adenoviruses" (H.S. Ginsberg, Editor, Plenum Press, 1984). Zhang Declaration, ¶15. Relevant excerpts from these texts are attached as Exhibit 2 to the Zhang Declaration.

The preceding descriptions and comparisons of adenovirus to hepatitis A virus provide substantial evidence that, due to the numerous dissimilarities, a teaching relating to one viral type

would not necessarily be applicable to the other. Thus, there is no *a priori* expectation that propagation of hepatitis A viruses would provide appropriate means for adenovirus preparations. Zhang Declaration, ¶12.

c. The wide range of viruses mentioned in Leu et al. do not belong to the family Adenoviridae.

The Examiner also asserts that Leu *et al.* teach a wide range of viruses. Applicants contend that none of the other viruses mentioned in the Leu *et al.* patent (column 5 lines 29-31), as cited by the Examiner, belong to the family *Adenoviridae.* In Examples 8 and 9, Leu *et al.* teach the propagation of varicella virus and mumps virus respectively. However, the Applicants point out to the Examiner that these viruses are distinct from that of adenovirus and belong to the Herpesviridae and the Paramyxoviridae respectively.

It is known in the art that both Herpesvirus and Paramyxovirus consist of an envelope with surface projections whereas adenovirus does not have an envelope. Thus, these viruses as compared to adenovirus require an isotonic osmolarity in order to achieve stability and prevent damage to their envelope membrane, whereas adenoviral stability may be achieved at relatively hypertonic osmolarity as it has no envelope. The replication cycle of Herpesvirus and Paramyxovirus is also distinct from that of adenovirus and involves proteins of the respective envelopes. Following entry into the host cell these viruses require specific enzymes, thymidine kinase and RNA-dependent RNA polymerase respectively, for transcription.

Therefore, the viruses used and mentioned in Leu *et al.* have structural and biological properties distinct from that of adenovirus, and in addition each has a specific time of infectivity. Zhang Declaration, ¶11.

"The mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination."

MPEP § 2143.01 citing *In re Mills,* 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). As discussed above, none of the references provides any reason for motivating their combination to render the invention obvious.

d. Leu et al. does not teach any benefit of infecting cells at a particular time frame

Applicants further point out that throughout the entire Leu *et al.* reference there is no indication regarding any benefit of employing the particular timing of infecting the cell culture at the time that is recited in the claims—that is, late log or early stationary phase of growth. The reference does not say that this timing leads, for example, to increased hepatitis A virus production. Further, Leu *et al.* do not address whether using the mid-log phase of growth, late log phase of growth, or stationary phase of growth to infect a cell culture would in any way be beneficial in achieving increased production of any other virus, including adenovirus. Consequently, there is no reason why a skilled artisan would turn to this particular aspect of the virus production process described in Leu *et al.* reference.

"[I]t is impermissible within the framework of 35 U.S.C. § 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art." *See also Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.,* 230 U.S.P.Q. 416 (Fed. Cir. 1986). The Action does not supply a reason for turning to the Leu *et al.* reference only for its timing of infection, and therefore, the basis for this rejection is impermissible. It appears that the Examiner is seeking to employ hindsight reconstruction to pick and choose among isolated disclosures in the prior art to render the instant invention as obvious. *See In re Fritch*, 972 F.2d 1260, 23 U.S.P.Q.2d 1780, 1784 (Fed. Cir. 1992). The Federal Circuit has repeatedly held that such hindsight reconstruction is an improper basis for a §103 rejection. *See id.*

Thus, given the reasons discussed above and provided in the declaration of Dr. Shuyuan Zhang, one of ordinary skill in the art would not be motivated to combine the teachings of Leu *et al.* with the teachings of Huyghe *et al.* or Zhang *et al.* to prepare an adenovirus of the instant invention. Accordingly, the rejection based on the combination of Leu *et al.* with that of Huyghe *et al.* and Zhang *et al.* does not meet a necessary criteria required to establish a *prima facie* case of obviousness.

C. Rejection of Claim 4 Under 35 U.S.C. §103 Is Overcome

The Action has rejected claim 4 over Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* in combination with the references of Garnier *et al.* or Perrin *et al.*. The Examiner states that claim 4 is drawn only to perfusing the producer cells only a portion of the time and does not recite glucose concentration levels and that Garnier *et al.* or Perrin *et al.* references teach all the limitations and provide motivation for perfusing with reasonable expectation of success. However, as stated above, the combination of Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* fails to make obvious claims 1-3, 8-25 and 29, and thus, other obviousness rejections based on this combination are improper for the reasons cited above. In this case, the additional references cited in the rejection of claim 4 do not rectify the defects of the original combination of references. Therefore, Applicants respectfully traverse the rejection of claim 4 as being obvious.

Claim 4 depends from claim 1, which recites "A process for preparing adenovirus, the process comprising: (a) preparing a culture of producer cells in a selected media; (b) infecting producer cells with adenovirus, wherein the producer cells are infected between mid-log phase of growth and stationary phase of growth; and (c) harvesting adenovirus from the cell culture. Thus, the claims of the instant invention are specific to adenoviruses. As discussed above, there

is no motivation to combine the teachings of Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* to practice the instant invention.

Furthermore, there would be no motivation to combine the teachings of Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* with the teachings of Perrin *et al.* as this latter reference teaches a rabies virus system. Thus, Perrin *et al.* in no way addresses the hurdle facing the combination of the Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* references, as the rabies virus—like the hepatitis virus—is quite distinct in their structure and biological properties from adenovirus. The rabies virus is an enveloped "budding" RNA-based rhabdovirus whereas adenovirus, as in the instant invention, is a DNA capsid based non-enveloped virus of an entirely different viral family—these viruses infect and grow differently and replicate differently. Zhang Declaration, ¶14. Further, the fact that Perrin *et al.* teach perfusion in the context of a rabies virus system does not provide any basis for employing the perfusion conditions for the rabies virus system with the other aspects of the cited references to practice the claimed invention, which is directed to adenovirus production. The Perrin *et al.* reference or any of the other cited references does not motivate their combination. Furthermore, a *prima facie* case of obviousness requires that there be a reasonable expectation of success of practicing the claimed invention based on the combination of references, and that expectation is, in fact, lacking, particularly because of the distinctions, discussed above, between a rabies virus and adenovirus.

The Action alternatively relies on the Garnier *et al.* reference, stating that in view of Leu *et al.*, Huyghe *et al.*, and Zhang *et al.*, the Garnier *et al.* reference provides the motivation to combine these references to practice the instant invention with a reasonable expectation of success. As discussed above, a proper *prima facie* case of obviousness based on Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* has not been established because there is no suggestion or

motivation to combine the first reference with the other two references. Thus, one would not look to this references in combination with Huyghe *et al.*, and Zhang *et al.* to practice the instant invention. The addition of the Garnier *et al.* reference to this combination of references does to cure the deficiencies of the original combination of references.

There remains no motivation to combine these four references to practice the instant invention as Garnier *et al.* relates only to a medium replacement strategy for improved production of a protein, protein tyrosine phosphatase 1C, and is not even concerned with virus production.

D. Rejection of Claims 26-28 Under 35 U.S.C. §103 Is Overcome

The Action rejects claims 26-28 as obvious over Leu *et al.* Huyghe *et al.*, and Zhang *et al.* in view of Graham *et al.* [1] The Action contends that Graham *et al.* in teaching 5% deoxycholate for cell disruption make obvious claims 26-28. Applicants traverse this rejection.

Claims 26-28 depend from claim 1, which, as stated *supra*, is not made obvious by Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* as this combination does not teach the claimed invention. The addition of the teachings of Graham *et al* does not cure the deficiencies of Leu *et al.* Huyghe *et al.*, and Zhang *et al.* The Graham reference is cited only for its teaching of 5% deoxycholate, which does not provide any motivation to combine the references of Leu *et al.*, Huyghe *et al.*, and Zhang *et al.* Therefore, claims 26-28 are not make obvious by the combinations of these four references.

In light of all the foregoing, Applicants respectfully request that the Examiner reconsideration and withdraw claims 1-4 and 8-29 as being obvious.

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[1] Applicants note that in the Office Action the Examiner cited reference (C7) as Graham *et al.* however, (C7) is Bussemaker *et al.* Applicants' arguments have assumed Graham *et al.* was the intended reference and consequently addressed the rejections accordingly.

E. Conclusion

Applicants believe that the present document is a full and complete response to the Office Action dated October . In conclusion, Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance, and such favorable action is respectfully requested.

The Examiner is invited to contact the undersigned Attorney at (512) 536-3081 with any questions, comments or suggestions relating to the referenced patent application.